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Positive Effects of Language Treatment for the Logopenic Variant of Primary Progressive Aphasia

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Abstract Despite considerable recent progress in understanding the underlying neurobiology of primary progressive aphasia (PPA) syndromes, relatively little attention has been directed toward the examination of behavioral interventions that may lessen the pervasive communication problems associated with PPA. In this study, we report on an individual with a behavioral profile and cortical atrophy pattern consistent with the logopenic variant of PPA. At roughly two-and-a-half years post onset, his marked lexical retrieval impairment prompted administration of a semantically based intervention to improve word retrieval. The treatment was designed to improve self-directed efforts to engage the participant's relatively preserved semantic system in order to facilitate word retrieval. His positive response to an intensive (2-week) dose of behavioral treatment was associated with improved lexical retrieval of items within trained categories, and generalized improvement for naming of untrained items that lasted over a 6-month follow-up interval. These findings support the potential value of intensive training to achieve self-directed strategic compensation for lexical retrieval difficulties in logopenic PPA. Additional insight was gained regarding the neural regions that supported improved performance by the administration of a functional magnetic resonance imaging protocol before and after treatment. In the context of a picture-naming task, post-treatment fMRI showed increased activation of left dorsolateral prefrontal regions that have been implicated in functional imaging studies of generative naming in healthy individuals. The increased activation in these frontal regions that were not significantly atrophic in our patient (as determined by voxel-based morphometry) is consistent with the notion that neural plasticity can support compensation for specific language loss, even in the context of progressive neuronal degeneration.

Keywords PPA · Rehabilitation · Anomia · Lexical retrieval · fMRI · Voxel-based morphometry

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Introduction

It is now well known that slowly progressive language impairment often heralds the onset of neurodegenerative disease that ultimately reveals itself as a form of frontotemporal dementia or Alzheimer disease (Hodges et al. 1992; Grossman et al. 1996; Neary et al. 1998; Mesulam et al. 2008). In fact, the progression of marked word-finding or speech production difficulties often prompts an individual's initial quest to determine the underlying problem and to seek treatment (Taylor et al. 2009; Sapolsky et al. 2011). Over the past several decades, considerable attention has been directed toward characterizing the clinical features of such individuals with primary progressive aphasia (PPA), and the associated patterns of cortical atrophy/hypometabolism (Mummery et al. 2000; Mesulam et al. 2003; Gorno-Tempini et al. 2004, 2008; Kertesz 2005; Amici et al. 2006). As a result, there is now good consensus regarding the diagnostic criteria for three distinct primary progressive aphasia (PPA) variants, and histopathological evidence of specific neurodegenerative pathology associated with each (Gorno-Tempini et al. 2011). Specifically, the characteristic speech and language profiles of nonfluent/agrammatic, semantic, and logopenic variants of PPA have been established.

The three PPA variants are distinguished by features of speech production, confrontation naming, comprehension ability, repetition skills, reading/spelling profiles, and the status of conceptual knowledge about objects and people. In brief, the semantic variant of PPA is characterized by anomia and comprehension deficits in the face of fluent speech production and preserved repetition abilities (Hodges et al. 1992; Warrington 1975). In contrast, the spoken output of individuals with the nonfluent/agrammatic variant of PPA is marked by effortful and halting speech production and/or a reduction in grammatical complexity of utterances (agrammatism), but conceptual knowledge and single-word comprehension are relatively preserved (Grossman et al. 1996; Hodges and Patterson 1996; Clark et al. 2005). The third, and most recently recognized PPA subtype, is the logopenic variant, which is characterized by marked word retrieval deficits in spontaneous speech and on confrontation naming tasks and impaired sentence repetition skills (Gorno-Tempini et al. 2008; Mesulam et al. 2008; Henry and Gorno-Tempini 2010). Relative to semantic dementia, conceptual knowledge and comprehension skills are better preserved in the logopenic variant. Furthermore, in contrast to nonfluent PPA, motor control for speech is spared and there is no evidence of agrammatism (Gorno-Tempini et al. 2011). Overall, the paucity of verbal output in the logopenic variant results in a fluency profile that is intermediate between the semantic and nonfluent subtypes.

From a neuroanatomical perspective, structural and functional imaging data confirm distinct regions of cortical atrophy/hypometabolism associated with each PPA subtype (Amici et al. 2006; Gorno-Tempini et al. 2006; Kang et al. 2010). The semantic variant is associated with left greater than right anterior temporal lobe atrophy/hypometabolism (Mummery et al. 2000; Hodges et al. 2004), whereas the nonfluent/agrammatic variant is associated with predominant abnormalities in the left posterior frontal and insular cortex (Grossman et al. 1996; Josephs et al. 2006; Nestor et al. 2007). In contrast, the logopenic variant is associated with left posterior perisylvian temporo-parietal atrophy/hypometabolism.

As the understanding and classification of PPA subtypes have advanced, attention has been directed toward the question of whether behavioral intervention may serve to improve or maintain speech/language performance, or to slow the rate of decline (Taylor et al. 2009; Sapolsky et al. 2011). To date, case reports and single-subject experimental research provide descriptions of behavioral intervention attempts with about 20 individuals with PPA. As might be expected, the specific PPA variant was not always established, but the descriptive information often suggests the probable subtype. The semantic variant of PPA has received the most attention, with treatment typically directed toward improving lexical retrieval for specifically targeted items (Graham et al. 1999; Jokel et al. 2006; Henry et al. 2008a; Green Heredia et al. 2009; Jokel et al. 2010). An item-specific response to treatment has been the most common outcome, indicating that despite the progressive degradation of semantic knowledge, it is possible to improve lexical access for trained items (Graham et al. 2001; Green Heredia et al. 2009; Jokel et al. 2010; Dressel 2011). In some instances, however, the response to treatment in semantic dementia has been quite modest in comparison with other PPA variants (Henry et al. 2008b; Newhart et al. 2009). Unfortunately, long-term retention of retrained skills has been limited, and in some instances there has been evidence that relearning appeared to rely on episodic, rather than semantic, memory (Graham et al. 1999; Snowden and Neary 2002), thus constraining the functional value of treatment because of its contextual specificity.

In contrast to the semantic variant, individuals with nonfluent/agrammatic PPA have the advantage of relatively well-preserved semantic knowledge, so the prognosis for retraining lexical retrieval should be somewhat better. Several documented cases have shown significant improvements on targeted items but, to date, there is no strong evidence of lasting effects over subsequent months (McNeil et al. 1995; Schneider et al. 1996; Jokel et al. 2009; Marcotte and Ansaldo 2010). In addition, the progressive impairment of speech production in the nonfluent variant may severely limit spoken language over time, so treatment may shift to a focus on supported, nonverbal communication to accommodate the changing needs of the individual (Murray 1998).

The most recently identified variant, logopenic PPA, has received little attention with regard to behavioral intervention for language decline. Given that individuals with the logopenic variant have relatively preserved semantic knowledge and the motor control for speech remains adequate, there should be good potential to benefit from behavioral treatment, particularly in the early stages. Recent evidence has shown that Alzheimer's disease is the most probable underlying etiology of the logopenic variant (Mesulam et al. 2008; Rabinovici et al. 2008), so ultimately, memory impairment is to be expected, but not until the mid to later stages of the disease process. A recent treatment study demonstrated the ability of an individual with logopenic PPA to relearn spoken and written names of targeted items, and also demonstrated some generalized improvement in the retrieval of untrained words (Newhart et al. 2009). These outcomes are encouraging, but there was no long-term follow-up reported for this case, so the durability of the treatment effects was not documented.

As behavioral interventions for PPA are considered, the obvious question emerges as to whether or not the time spent on language rehabilitation is worthwhile, given the progressive nature of the underlying diseases. Some case reports suggest that even relearning of a specific corpus of personally relevant words provides adequate benefit to the individual for the time and effort invested (Graham et al. 1999; Henry et al. 2008b). It is not clear, however, how participants perceive the modest benefit and rapid loss of regained skills in other reported cases (e.g., Bier et al. 2009). Ideally, the effects of treatment would generalize across items and contexts, and the benefits would persist over time to some extent. Concern about these issues motivated the design and implementation of the treatment study reported here. Specifically, we examined the outcomes from treatment provided to an individual in the early stages of the logopenic variant of PPA. Treatment was administered over a short period of time (2 weeks), with maintenance performance sampled at 3 weeks, 4 months, and 6 months after treatment. We were particularly interested to determine whether the individual could be trained to intentionally exploit his residual semantic knowledge and to apply lexical retrieval strategies to untrained words and contexts (i.e., discourse production). To do so, we built upon the success of a semantically based lexical retrieval treatment approach that we examined in an earlier study with two individuals with PPA and one individual with anomic aphasia due to stroke (Henry et al. 2008b). In that study, an intensive, 2-week treatment period using generative naming tasks (category fluency) combined with semantic elaboration training resulted in positive outcomes for the stroke patient and the individual with PPA with preserved semantic knowledge, but only modest benefit in the individual with a documented semantic impairment. The intensive treatment schedule and the effortful lexical retrieval training task (generative naming) had the benefit of realizing relatively rapid behavioral changes, and minimized the effects of the disease progression during the treatment interval. In the present study, we aimed to examine the durability of outcomes for a longer period of time (6 months), and also sought additional information regarding the underlying mechanism of improved language performance in the participant by conducting functional magnetic imaging during a naming task before and after treatment.

Materials and Methods

Participant

Mr. W was a 77-year-old right-handed man with a two-and-a-half year reported history of language decline. A retired accountant, Mr. W had more than 15 years of education and had remained involved in finance and computer programming during his retirement. He also had a professional background in music, and still played the accordion regularly. He lived independently and was the patriarch of a large extended family with 17 grandchildren. Mr. W drove himself unaccompanied to most assessment and treatment sessions, and participated in active daily routines and hobbies including tennis and gardening.

At the time of the initial evaluation, Mr. W's primary complaint was difficulty "coming up with the words," even for familiar things, such as musical instruments or the names of his grandchildren. His conversational speech was marked by anomia, prolonged pauses, verbal fillers, and slowed speaking rate. The working diagnosis from Mr. W's primary care physician and consulting neurologist was "primary progressive aphasia." At the outset of this study, he was taking Aricept.

Both Mr. W and his adult daughter completed the *Neuropsychiatric Inventory Questionnaire* (adapted from Kaufer et al. 2000) to determine whether any significant behavioral changes (e.g., delusions, hallucinations, depression, and anxiety) were noted. Neither Mr. W nor his daughter endorsed any of the psychiatric symptoms on this questionnaire. In addition, they both completed the *Instrumental Activities of Daily Living Scale* (Lawton and Brody 1969), which documents an individual's ability to complete a range of activities of daily living (e.g., using the telephone, handling medications, and managing finances). Their responses confirmed that Mr. W was fully functional and independent for daily activities.

Initial Assessment

A comprehensive assessment was completed over the course of several visits to examine speech and language abilities, nonverbal cognitive performance, and overall behavioral competence. During the first visit, a pure tone audiogram confirmed hearing within normal limits up to 4,000 Hz, with a sloping, bilateral high frequency hearing loss detected at 6,000–8,000 Hz. His hearing was adequate for behavioral testing in a quiet room without amplification.

Speech and Language Assessment

Mr. W's speech production was unimpaired and there was no evidence of motor control difficulties for speech. With regard to language, his performance on the *Western Aphasia Battery* (*WAB*; Kertesz 1982) was consistent with mild anomic aphasia (Aphasia Quotient=90.6). His spontaneous speech was relatively fluent with normal syntactic structure, but marred by word-finding difficulty. Auditory comprehension was good, but repetition of sentences was mildly impaired. Mr. W's naming impairment was particularly evident on the *Boston Naming Test* (BNT; Kaplan et al. 2001) on which he correctly named only 24 of 60 items. During instances of anomia, it was not uncommon for Mr. W to provide appropriate descriptive information about a pictured item, but this semantic circumlocution rarely helped him to retrieve the correct name. An additional measure of naming ability was obtained on a 64-item colored picture-naming test that included 32 living things and 32 nonliving things (adapted from Garrard et al. 2002). On this test, Mr. W showed a category-specific deficit manifested by significantly greater difficulty naming living, compared to nonliving, items (18/32 vs. 29/32, chi-square= 8.01, $p<0.005$; see Table 1). Word retrieval difficulties were also marked on the category fluency task for animal naming in 1 min (see Table 1). In contrast, his ability to generate

Table 1 Pre–post-treatment scores with cutoff/normative values for each measure

Assessment (possible)	Norms for age, score (SD)	Before treatment		After treatment			
		Pre-Tx 1	Pre-Tx 2	Immed. post-Tx	3-week post-Tx	4-month post-Tx	6-month post-Tx
MMSE (30)	≥25	25	_24_	25	–	–	26
Ravens CPM (36)	29.7[a] (4.57)	29	29	26	–	–	25
Semantics							
PPT pictures (52)	50.8[a] (1.03)	48	_47_	48	–	–	49
PPT written (52)	51.0[a] (0.94)	48	–	–	–	–	–
Aphasia quotient (100)	≥93.8	_90.6_	_91.3_	_92.2_	–	–	_89.8_
Comprehension—sentence							
PALPA 55 spoken Sent-pic match (60)	56.99[b] (0.81)	–	58	_55_	–	–	_56_
Confrontation naming							
BNT (60)	53.4[c] (4.9)	_24_	_26_	_31_	_37_**	_32_	_34_*
PNT (175)	171.1[d] (3.6)		_140_	_150_*	_155_**	_154_**	_152_*
AZ living (32)	31.2[a] (1.03)	_18_	_23_	28[e]	30[e]	–	–
AZ nonliving (32)	31.8[a] (0.42)	29	29	30	28	–	–
Generative naming							
Animals	16.1[f] (4.0)	_9_	_7_	_11_	_11_	_9_	13
FAS (letter fluency)	34.8[f] (12.8)	33	27	35	–	–	27
Discourse analysis							
Words per minute	157.5[g] (26.6)	–	_112_	116[e]			120[e]
Informativeness, %CIUs	79%[g] (12.3%)	–	65%	76%	–	–	73%
Efficiency, CIUs/min	127.6[g] (30.08)	–	_72.6_	88[e]	–	–	87.3[e]

*$p<0.05$; **$p<0.01$ denotes significant improvement relative to pre-treatment (Pre-Tx 2), McNemar test. Values in italics indicate performance significantly below test cutoff score, or below performance of a relevant control sample using one-tailed t test according to procedures detailed by Crawford et al. (2011). Aphasia Quotient is from Western Aphasia Battery

BNT Boston Naming Test, *CIUs* correct information units, *CPM* Coloured Progressive Matrices, *MMSE* Mini-Mental Status Examination, *PALPA 55* Spoken Sentence-Picture Matching, *PNT* Philadelphia Naming Test, *PPT* Pyramids and Palm Trees Test

[a] Normative data from University of Arizona Aphasia Research Project; 10 healthy adults, mean age=76.6 (5.44) Range 69–85; mean education= 16.1 (2.77) Range 12–22; Male:Female 4:6

[b] Normative data from PALPA manual (Kay et al. 1992)

[c] Normative data from Borod et al. (1980)

[d] Normative data from PNT: (Myrna Schwartz, personal communication) control subjects; n=12, mean age=67.5 (SD=5.1), education=13.6 (SD=1.6); Male:Female=3:9

[e] Improved from significantly below normative performance levels to within the normal range

[f] Normative data for verbal fluency from Tombaugh et al. (1999)

[g] Normative data from Nicholas and Brookshire (1993) Birthday Picture Description. Control group mean age=71.4 years

words beginning with the letters F, A, and S (i.e., letter fluency) was relatively preserved.

Mr. W's marked impairment of semantically guided lexical retrieval was observed in the context of relatively preserved semantic knowledge. As shown in Table 1, he performed roughly within the normal range on both the picture and written versions of the *Pyramid and Palm Trees Test, (PPT*; Howard and Patterson 1992). His relatively intact comprehension of single words was confirmed on spoken-word to picture match (39/40 correct) and written-word to picture match (39/40 correct) subtests (47 and 48) from the *Psycholinguistic Assessment of Language Processing in Aphasia* (PALPA; Kay et al. 1992).

With regard to phonological processing, Mr. W performed within normal limits on a battery of tasks including rhyme judgment, phoneme replacement, minimal pair discrimination, and word/nonword repetition. Although his sentence repetition skills were mildly impaired, his digit span (forward) was near the mean for individuals aged 70–74 (raw score=7; 47th percentile; Wechsler Memory Scale-Revised; Wechsler 1984).

Written language skills were examined using the Arizona Battery for Reading and Spelling (ABRS, n.d.). Single-word reading was relatively preserved (78/80 correct for words; 19/20 for nonwords). Spelling was impaired to some extent (63/80 correct), with most errors made on low frequency, irregularly spelled words. His relatively strong phonological skills were evident by the phonologically plausible spelling errors (e.g., *cercuit* for circuit; *shure* for sure), and his ability to generate appropriate spellings for nonwords (20/20). There were no problems regarding the visual processing of orthographic stimuli as judged on tests of letter-form knowledge (e.g., letter orientation judgments and lexical decision tasks).

Measures of General Cognitive Function

The marked anomia and mild written language impairment were observed in the context of relatively preserved memory and nonverbal cognition. His performance on the *Mini-Mental Status Examination* (MMSE; Folstein et al. 1975) was just within normal limits (25/30) and confirmed his orientation to time, place, and day. As expected, however, Mr. W made errors on some items with verbal demands (e.g., remembering three words, and phrase repetition). Nonverbal visual problem solving was well preserved as measured by the *Raven's Coloured Progressive Matrices* (Raven et al. 1990). On the Trail Making Test (Reitan and Wolfson 1985; Tombaugh 2004), he completed both Trails A and B without error, but the time to complete the tasks was slower than expected for his age and education (Trails A=70 s, < 10th percentile; Trails B=144 s, ~20th percentile).

Second Pre-treatment Assessment

Three months after the initial assessment, Mr. W was re-evaluated immediately prior to the initiation of behavioral treatment. As shown in Table 1, his performance was relatively consistent with the initial assessment. Some additional language measures were implemented to further evaluate comprehension and lexical retrieval. The spoken sentence-to-picture match subtest 55 of the PALPA confirmed little difficulty in sentence comprehension. The 175-item *Philadelphia Naming Test* (*PNT*; Roach et al. 1996) further documented Mr. W's naming impairment (140/175 correct). On a more functional speaking task of describing a pictured scene (the "birthday party" from Nicholas and Brookshire 1993), Mr. W's spoken narrative was relatively accurate with well-formed sentences, but his speaking rate was slow and included notable word-finding pauses. His spoken narrative was analyzed using standard procedures to quantify speaking rate, informativeness (defined as the proportion of utterances with meaningful content) and efficiency (the amount of content conveyed per minute) (Nicholas and Brookshire 1993). As shown in Table 1, Mr. W's rate of speech was slow relative to age-matched controls (112 vs. 157 wpm), but the amount of information conveyed relative to the total number of words (correct information units/total word count) was not significantly below the normal range (65% vs. 79%). With regard to efficiency, the amount of information that he conveyed per minute was significantly less than expected (72.6 vs. 126 CIUs/min).

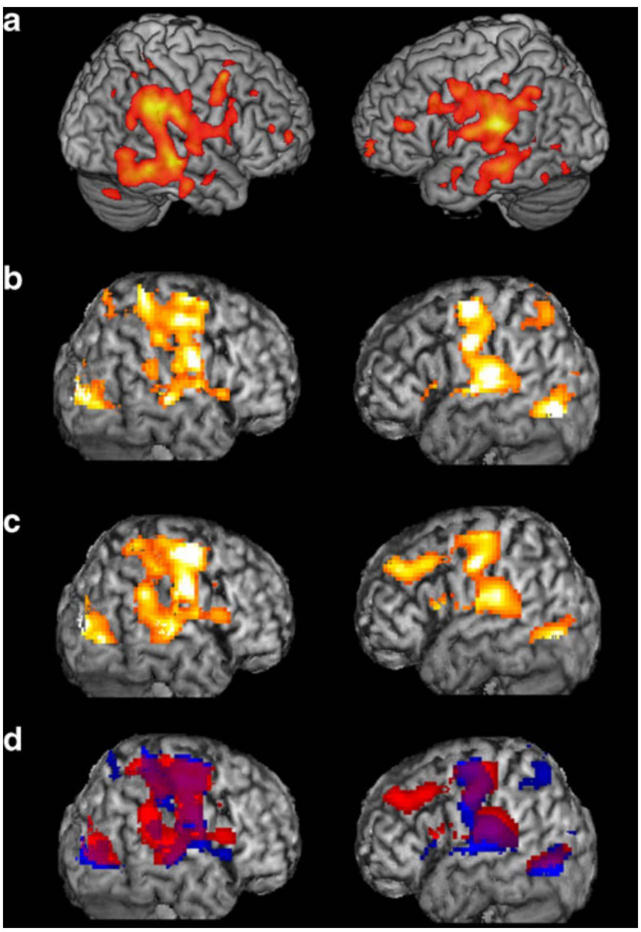
Brain Imaging

A high-resolution T1-weighted MRI brain scan was acquired on a 3 Tesla (3 T) General Electric Excite MRI scanner (Milwaukee, Wisconsin) using a 3D inversion recovery (IR) prepped spoiled-gradient-echo (SPGR) sequence with the following parameters: repetition time, TR=7.4 ms; echo time, TE=3.0 ms; inversion time, TI=500 ms; flip angle=15; field of view (FOV)=26×26×19 cm; matrix size=256×256×124; NEX=1; acquisition time, TA=approximately 8 min. Resulting voxel dimensions were 1×1×1.5 (S/I, A/P, R/L, respectively). Voxel-based morphometry (VBM) was implemented to analyze patterns of regional cortical atrophy in Mr. W relative to the brains of 15 healthy control subjects (mean age=67.8 years, SD=8.5; education=16 years, SD=2.7; mean MMSE=29.2, SD=0.9).

Prior to processing, T1 images were evaluated for quality, including motion and other artifacts that could contribute to systematic registration biases. Brain images for the patient and normal controls were segmented into gray matter, white matter, and cerebrospinal fluid using the automated segmentation routines in SPM5 (Statistical Parametric Mapping; Wellcome Department of Cognitive

Neurology; Ashburner and Friston 2005), augmented by the VBM5 toolbox available at http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/. Sample-specific customized priors were used. Spatial normalization was accomplished using procedures described by Good et al. (2001) and images were smoothed with a 12 mm full-width-half-maximum (FWHM) Gaussian kernel. The VBM analysis was thresholded for significance at $p<0.01$, with false discovery rate (FDR) correction applied. As shown in Fig. 1a, bilateral cortical atrophy was prominent in the posterior perisylvian regions and mid-lateral temporal lobes (see Fig. 1a).

A functional MRI brain scan was also obtained immediately before treatment using a picture-naming task presented using a long trial event-related design. The task involved naming 90 color pictures (Rossion and Pourtois 2004) that were not used in the treatment study. Individual pictures were presented for 5 s, followed by a fixation cross for 15 s, with an inter-trial interval of 20 s (Dale 1999). Two functional imaging runs (~10 min each) were implemented using echo planer imaging (EPI) with 32 slices per volume, 3 mm slice thickness, 2 s repetition time (TR), 35 ms echo time (TE), FOV of 24 cm, flip angle of 90° and matrix size of 64×64. Using SPM5, functional images were normalized and smoothed using a 10-mm (FWHM) Gaussian kernel, and the main effect of naming versus rest condition was computed using a t test thresholded voxelwise at $p<0.05$, corrected for multiple comparisons per familywise error (FWE; Nichols and Hayasaka 2003).



a. Regions of significant atrophy relative to 15 normal controls (p <.01 FDR).
b. Significant fMRI activation on picture naming task before treatment (p<.05 FWE).
c. Significant fMRI activation on picture naming task after treatment (p<.05 FWE).
d. Overlay of regions of significant fMRI activation prior to treatment (blue), after treatment (red), and at both time points (purple).

Fig. 1 Neuroimaging results from **a** voxel-based morphometry displayed on template brain, and functional magnetic resonance imaging results displayed on participant brain showing significant activation **b** before treatment, **c** after treatment, **d** overlay of pre–post-treatment fMRI results

The resulting statistical images, displayed in Fig. 1b, show extensive bilateral activation in pre- and post-central gyri and posterior superior temporal gyrus, as well as bilateral activation in ventro-lateral temporo-occipital cortex and in both superior parietal lobules. In comparison to the functional imaging studies of naming in healthy adults (e.g., Bookheimer et al. 1995; Gold and Buckner 2002; Abrahams et al. 2003; Price et al. 2005), Mr. W's pattern of activation was anomalous in several respects. Most notable was the extensive right hemisphere activation, the recruitment of the left superior parietal lobule, as well as the striking paucity of activation in the left frontal opercular cortex (Brodmann areas 44/45) that is reliably engaged in functional imaging studies of naming. Although older adults typically show greater bilateral activation relative to younger adults on naming tasks (Wierenga et al. 2008), the extensive right hemisphere activation observed in Mr. W was clearly outside the normal range. Of the regions in the left hemisphere language network engaged by older adults on picture-naming tasks (Wierenga et al. 2008), Mr. W showed activation in the sensorimotor cortex, superior temporal gyrus, and small portions of the inferior frontal gyrus.

In summary, the pre-treatment behavioral evaluation confirmed that Mr. W had significant impairment of lexical retrieval abilities in the face of relatively spared semantic knowledge, syntactic skills, motor control for speech, and nonverbal cognitive functioning. This profile was consistent with the logopenic variant of PPA, and the VBM analysis of his structural MRI confirmed a cortical atrophy pattern consistent with this diagnosis. Functional MRI during picture naming revealed significant bilateral activation including regions not typically activated by healthy adults, but decreased recruitment in left prefrontal regions that are reliably activated in normal individuals. Mr. W was interested and motivated to participate in behavioral treatment to improve his word retrieval.

Treatment Method

Generative naming tasks (by semantic category) were used to probe and to train lexical retrieval. Six categories were trained (three living and three nonliving), and six semantically matched categories were probed but not trained (see categories in Fig. 2). Categories were selected on the basis of picturability (to allow use of colored photographs to be used for training items during treatment), personal relevance to Mr. W, and his pre-treatment performance. The treatment schedule consisted of 2-hour treatment sessions, 6 days per week for 2 weeks, along with approximately 1 h of daily homework.

It is important to note that the generative naming task, that is, the repeated retrieval of words from a semantic category under a time constraint, is typically a more demanding task than word retrieval in conversation or confrontation naming. It was used for the training protocol as a means to tax lexical retrieval procedures with the intention of improving performance in more functional contexts. In other words, improvement on generative naming tasks was only of interest as it served to facilitate improved word retrieval on confrontation naming and in spoken discourse.

As depicted in Fig. 2, two probes were obtained for each of the 12 categories (six to be trained; six not trained) before initiating any treatment, and repeated multiple baseline probes were collected for all categories after training was initiated. Training began for the first category (vegetables) on Day 1, after a third pre-treatment probe. Each trained category received clinician-administered treatment for two consecutive sessions (marked in black on Fig. 2). Training began with presentation of about 30 colored photographs of example items from the category in training, with written labels available for each item. After multiple accurate naming attempts for the pictured items, the labels were removed and naming attempted again. Subsequent tasks focused on elaboration of the semantic features of items, including sub-categorization and comparing/contrasting items within a category. For example, tools might be sorted into groups, such as “things that pound” and “things that cut.” The semantic tasks were followed by repeated generative naming attempts of the targeted category. In order to promote cognitive effort and decrease the likelihood of rote memorization of items, Mr. W was encouraged to name items within the semantic category that were not pictured, as well as those that were pictured.

The second treatment day for a given category was used to train semantic elaboration strategies as a means to prompt lexical retrieval. The approach was consistent with semantic feature analysis treatments, and included elaboration of attributes (properties of the items), typical functional use of items, context (where the item is found), listing of similar items (coordinate members of the category), and identification of the superordinate category (Lowell et al. 1995; Boyle 2004; Henry et al. 2008b). Structured homework tasks included reviewing the labeled pictures of items from the target category, written generative naming by subcategories, and filling out schematic diagrams

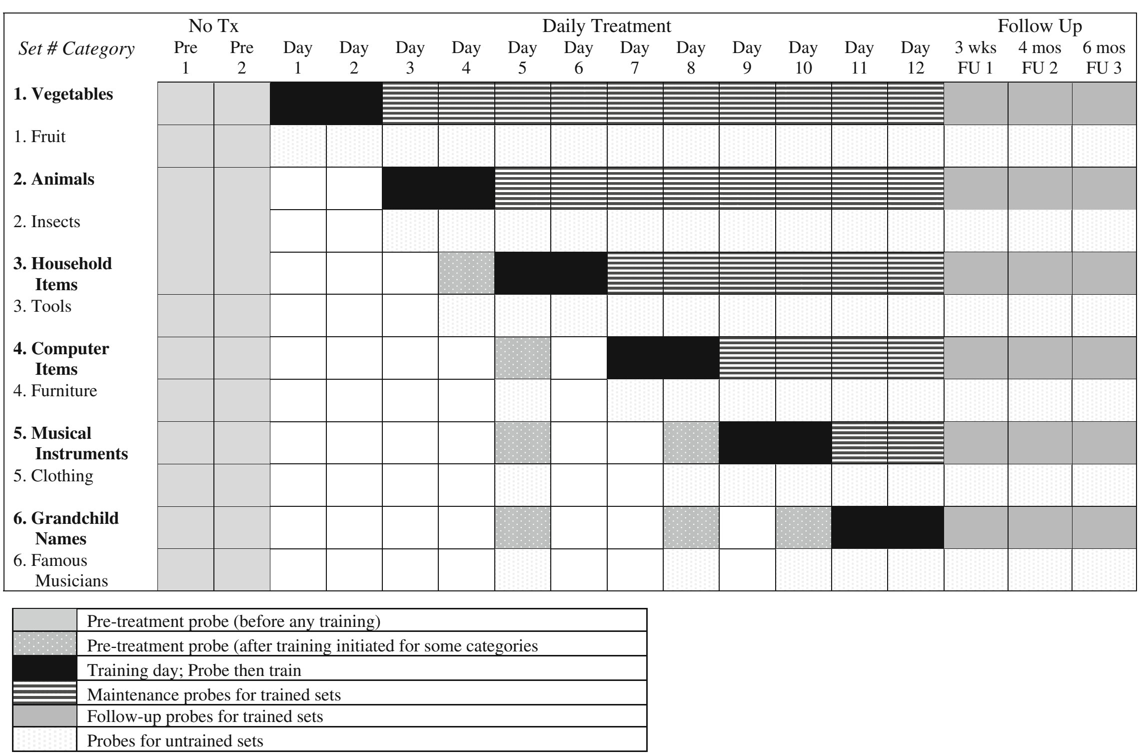


Fig. 2 Schedule of generative naming probes for trained (*in bold*) and untrained semantic categories and treatment schedule

depicting subcategory members, and common or unique semantic features. For example, musical instruments might be grouped by "brass," vs. "woodwind," vs. "percussion." or by "marching band" vs. "orchestra" instruments.

At the beginning of each session, the previous day's trained and the matching untrained categories were probed, and additional probes were conducted for other categories as indicated in Fig. 2. After the completion of the 2-day training period for one semantic category, post-treatment probes were conducted at the beginning of the next session, as treatment shifted to the next category. Maintenance probes for each category were collected as treatment progressed, and all categories were probed at the end of the 2-week treatment period. Additional post-treatment follow-up probes were collected at 3 weeks, 4 months and 6 months after the end of treatment. The fMRI protocol was repeated after the 2 weeks of treatment, and again after the 3-week follow-up.

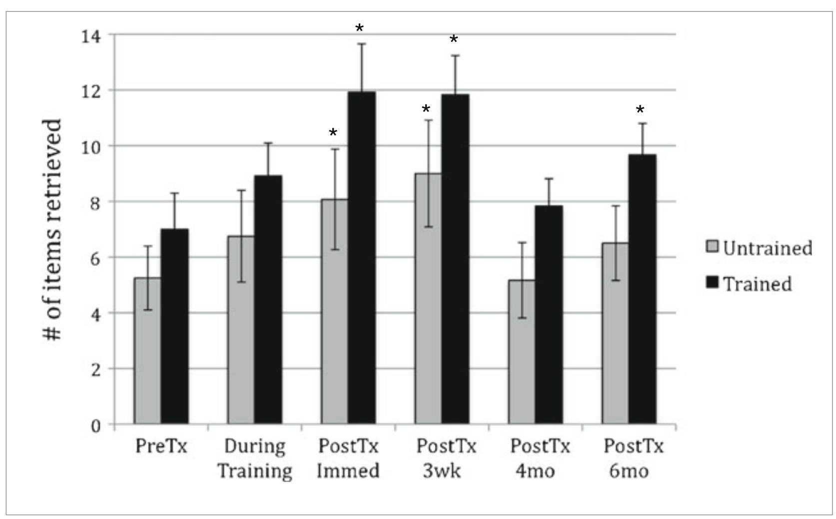
Results

Mr. W attended all 12 treatment sessions conducted over 2 weeks. He brought completed homework assignments to each meeting, confirming additional time spent training at home. In total, Mr. W received 24 h of clinician-administered treatment supplemented by approximately 15 h of homework. Mr. W's health remained stable over the course of treatment, but it should be noted that at the time of the 4-month follow-up after treatment, he complained of trouble with medication side effects and had interrupted his Aricept regimen for several weeks. By the 6-month follow-up visit, he reported that his medication schedule had been re-established, and that he was feeling better.

Direct Treatment Effects

For clarity and ease of display, the multiple baseline data for the six trained and six untrained categories were collapsed by averaging performance on probes during specific time periods (e.g., before treatment, during treatment for a given category, and post-treatment probes immediately after treatment and at follow-up). As shown in Fig. 3, Mr. W improved his ability to retrieve exemplars for the trained categories, and he also improved his performance on untrained categories. It was evident that, after treatment was initiated, Mr. W used semantically based strategies to assist him on the generative naming probes. For example, when naming vegetables, he prompted himself by saying, "Okay, now salad vegetables… Next, what goes in a stew?" Or when naming computer-related terms, he said, for example, "Software programs.... What about hardware… And now the Internet…"

Generalization of the semantic elaboration and self-cueing strategies was a favorable outcome, and resulted in a slight upward drift in performance on pre-treatment probes for untrained categories. For that reason, treatment outcomes were compared to the generative naming probes taken prior to initiation of *any* treatment (i.e., the first two pre-treatment probes for all categories). As shown in Fig. 3, the post-treatment generative naming performance was significantly improved for trained and untrained categories



* p < .05, Wilcoxon test.

Fig. 3 Average number of words retrieved on 1-minute generative naming tasks for untrained (*UnTx*) and trained (*Tx*) categories during pre-treatment probes, training phase, post-treatment probes immediately after treatment, and post-treatment follow-up probes at 3 weeks, 4 months, and 6 months after treatment. Table below shows *d*-statistic values associated with change in level of performance compared to pre-treatment phase

Time	Immed. PostTx		PostTx 3wk		PostTx 4 mo		PostTx 6mo	
Condition	*UnTx*	*Tx*	*UnTx*	*Tx*	*UnTx*	*Tx*	*UnTx*	*Tx*
d statistic	1.44	2.31	3.54	2.17	-0.62	0.35	0.38	1.51

immediately after treatment was implemented and at the 3-week follow-up (Wilcoxon rank sum test $W=-21$, $n=6$, $p<0.025$). Performance on the trained categories was also significantly better than pre-treatment performance at the 6-month follow-up (Wilcoxon $W=-19$; $n=6$, $p<0.05$). A slight drop in performance was noted at the 4-month follow-up when Mr. W was not feeling well.

In order to provide a standardized index of change in Mr. W's level of generative naming performance in response to treatment, effect sizes were calculated (*d* statistic) for each category and weighted averages were computed for the trained and untrained categories at each of the post-treatment time points (See Beeson and Robey 2006, for details regarding effect size calculation for single-subject multiple baseline data.). The effect sizes are displayed below Fig. 3 and reflect the improvement immediately after treatment and at the 3-week follow-up, and an impressive *d*-statistic of 3.54 reflecting the level of change for the untrained categories at 3 weeks post-treatment. The effect size values serve to quantify the generalized improvement of lexical retrieval in the timed verbal fluency task, and indicate the more lasting effects at 6 months post-treatment for the trained categories.

Post-treatment Assessment and Generalization Effects

As indicated in Table 1, Mr. W's improvements in generative naming occurred in the context of relatively stable performance on several measures of language and nonverbal cognitive performance over the course of treatment and the following 6 months. Specifically, his MMSE score and performance on the picture version of the semantic relations test (PPT) showed little change. His aphasia quotient declined only slightly (roughly one point), but it was interesting to note that the score reflected a slight improvement in naming and a small decline in sentence repetition skills. The latter was consistent with the logopenic PPA profile wherein repetition skills decline over time. His performance on the visual problem-solving task (i.e., Ravens CPM) declined some (from 29 to 25), but was still roughly within normal limits.

In contrast to relatively stable or slightly declining performance on other tasks, Mr. W showed significant improvement on three measures of confrontation naming for untrained items (see Table 1). On the 60-item BNT, he improved from a pre-treatment score of 26 to sequential post-treatment scores of 31 to 37 to 32 to 34. Similarly, naming performance improved on the *Philadelphia Naming Test* (175 possible) from 140 (immediately prior to treatment) to 150 to 155 to 154 to 152, on the subsequent post-treatment probes. By-item analyses using the McNemar test indicated that the post-treatment BNT scores at 3-weeks and 6-months post-treatment were significantly improved relative to pre-treatment ($p<0.002$; $p<0.02$), and all of the post-treatment PNT scores reflected significant improvement relative to pre-treatment ($p<0.05$, $p<0.002$, $p<0.007$, $p<0.02$). Significant improvement was also documented for naming "living" things, which was disproportionately impaired prior to treatment (see Table 1). As noted during pre-treatment assessment, Mr. W often provided semantic information when trying to recall the name of an item; however, after treatment, this strategy resulted in instances wherein the semantic elaboration served to self-cue the correct response.

Discourse Analyses

Post-treatment discourse production showed improvement in speaking rate (from 112 to 116 to 120 wpm), and the number of correct information units conveyed also increased over time. Thus, the overall efficiency of Mr. W's discourse improved in terms of the amount of correct (CIUs) per minute (from 72.6 to 88 to 87), and his post-treatment performance was within the normal range for his age (see Table 1).

Self-assessment of Change

In order to evaluate Mr. W's perspective on his lexical retrieval skills after treatment, he completed a self-assessment at the 3-week follow-up visit. Six questions were presented with a qualitative rating scale to indicate his perception of his abilities after treatment (compared to before treatment) using seven response options: a) A lot worse, b) Worse, c) Somewhat worse, d) Unchanged, e) Somewhat better, f) Better, and g) A lot better. Mr. W rated his overall confidence level regarding spoken communication and his ability to speak fluently as "a lot better." He rated his ability to name things, his overall speaking ability and his stress level during conversation as "better" after the treatment. He also reported that his ability to think of people's names and come up with words in conversation were "somewhat better." In post-treatment interviews, Mr. W excitedly praised the treatment as pivotal to his increased vocabulary and overall confidence in daily communication. He reported that his children were aware of his spoken language improvements, and two of his daughters independently reported improved conversational interactions in the months following treatment. One other source of confirmation of Mr. W's perceived benefit from treatment came from his unsolicited comments to several other individuals in a PPA support group, indicating that he had "re-learned around 150 vocabulary words."

Post-treatment fMRI

The pre-treatment fMRI protocol was re-administered to Mr. W in the week following completion of the 2-week behavioral intervention, and again at roughly 3 weeks post-treatment. The scans were processed in the same manner as the pre-treatment scans. Unfortunately, there was too much movement artifact from the 3-week follow-up scans to allow meaningful data analysis, so only the fMRI scans taken immediately after treatment were analyzed in relation to the pre-treatment scans. As shown in Fig. 1c, the fMRI results after treatment showed marked activation in the left dorsolateral prefrontal region that was not engaged during the pre-treatment scanning. This region is particularly evident in Fig. 1d (in *red*), which provides an overlay of the significant regions of activation during the pre- and post-treatment scanning sessions. A direct statistical comparison of the two scanning sessions confirmed that this activation in left middle frontal gyrus was significantly greater after treatment ($p<0.05$, FWE correction). Although there was some increase in Broca's area activation and its right hemisphere homologue, these did not reach significance in the direct pre–post-treatment comparison. The bilateral activation in the Rolandic and posterior perisylvian regions, as well as lateral temporo-occipital cortex remained relatively consistent with the pre-treatment scans. No longer evident was the strong activation in the left superior parietal lobule.

Discussion

We report here on the positive treatment outcomes in an individual with logopenic PPA who participated in an intensive 2-week treatment for lexical retrieval. His pre-treatment profile revealed a marked naming impairment on confrontation naming tests, verbal fluency tasks, and in conversation. Consistent with the logopenic variant of PPA, naming difficulty was evident in the context of relatively spared semantic knowledge, speech fluency, syntactic form, and auditory comprehension. This individual responded well to the semantically based treatment and showed significant improvements in naming on the training task (generative naming by semantic category) and also generalized to improved performance on standardized measures of confrontation naming. At a functional level, his narrative discourse reflected more efficient lexical retrieval after treatment, and he more closely approximated normal performance on a picture description task. Changes in post-treatment fMRI activation suggested the behavioral improvements were supported by increased reliance on left prefrontal cortex during word retrieval.

Relative to the existing PPA treatment literature, the improvements documented in this study are the strongest of those reported to date. Whereas other researchers have demonstrated item-specific improvements that persisted when retested up to 6 months, no other study has shown such a robust and persistent generalization effect. Green Heredia et al. (2009), for example, showed generalization to different pictures of the trained items, and Schneider et al. (1996) showed generalization that was constrained to specific transitive verb forms. In the present study, however, the participant improved naming for untrained items on two measures of confrontation naming (BNT and PNT), and in discourse production. It was clear that he was using semantically based self-cueing strategies when he encountered word-finding difficulties in a variety of contexts. In other words, he showed generalization of the lexical retrieval strategy, which had a more potent effect than item-specific treatment outcomes. Both the participant and his family reported a decrease in his language impairment and improved communication success.

The language profile associated with logopenic PPA is well suited to the semantically based treatment approach used here. The procedures included tasks that are implemented in other semantic feature analysis treatments wherein participants are encouraged to describe the attributes, function, categorical membership, etc. in order to strengthen semantic activation as a means to access the phonological representation. This semantic self-cueing approach has been shown by to improve lexical retrieval in individuals with stroke-induced aphasia for trained as well as untrained items (e.g., Lowell et al. 1995; Boyle 2004), and the generalization observed in our logopenic patient was consistent with those findings. In this study, and in Henry et al. (2008b), generative naming trials were also included as part of the treatment protocol. Of course, such tasks have limited functional value in daily life; that is, people are rarely required to name many members of a category under time constraints. However, such tasks provide a useful context for treatment because they require sustained, semantically guided lexical retrieval efforts.

The results from the fMRI provide converging evidence that Mr. W's naming improvements were associated with increased cognitive effort. The significant activation in left dorsolateral prefrontal regions observed after treatment is consistent with strategic planning and monitoring of lexical retrieval, as demonstrated in functional imaging studies of healthy adults engaged in verbal fluency tasks (Warburton et al. 1996; Perani 2003; Meinzer et al. 2009). Mr. W also showed activation in Broca's area, a region that is commonly engaged during naming tasks (Abrahams et al. 2003; Price et al. 2005; Wierenga et al. 2008), but the imaging results suggest greater reliance on left prefrontal regions that are more commonly involved in effortful lexical retrieval tasks that require higher levels of executive control. The VBM analysis indicated that these frontal regions were structurally healthy and available to support the more deliberate lexical retrieval efforts necessitated by the degradation of other regions of the language network.

To our knowledge, only two other studies of PPA treatment have examined pre–post-treatment changes using functional imaging (Marcotte and Ansaldo 2010; Dressel 2011). Marcotte and Ansaldo (2010) reported on the treatment outcomes from an individual with nonfluent PPA and imaging evidence of frontal lobe pathology. Following treatment to improve lexical retrieval, the post-treatment fMRI showed increased activation that was most notable in right hemisphere areas, so there was bilateral activation of superior and inferior parietal lobules. Increases in left hemisphere activity were restricted to subcortical gray matter (thalamus, putamen, and lateral globus pallidus), along with some increase in left superior and middle temporal gyri. This increased reliance on the right hemisphere and left temporal regions was a plausible compensation pattern in the face of frontal lobe pathology. The one other reported case of functional imaging before and after behavioral treatment involved the semantic variant of PPA (Dressel 2011). In this individual, improved lexical retrieval was associated with increased activation in the right temporal lobe. Our case with logopenic PPA also showed extensive bilateral activation during lexical retrieval trials, both before and after treatment, but the post-treatment changes were most notable in left prefrontal regions. Thus, he demonstrated increased reliance on structurally preserved left frontal executive regions to compensate for the lexical retrieval difficulties. In summary, each of the three cases demonstrated increased activation in cortical areas that are typically preserved for the specific PPA variant, and the participant in the present study showed the strongest left-lateralized change along with evidence that behavioral improvement was related to the engagement of frontal cortical regions that are also recruited by normal individuals in lexical retrieval tasks with high executive demands.

It is important to emphasize that the effortful daily training implemented in this study, combined with structured home practice, exceeds the demands placed on most individuals during language rehabilitation, and the intensity of effort may have been an important factor influencing the positive treatment outcome. We suggest that the active training and engaging of cognitively based lexical retrieval strategies may have a stronger influence on brain plasticity than more passive tasks that simply require reactive responses or repetition of spoken words. This point is important because there has been considerable attention in recent years directed toward exploring the value of errorless learning paradigms in individuals with aphasia (progressive or otherwise) (Fillingham et al. 2003; Frattali 2004; Fridriksson et al. 2006; Jokel et al. 2007; Jokel et al. 2010). Errorless learning paradigms were initially implemented with individuals with severely impaired episodic memory that limited their ability to learn compensatory strategies or to learn from their errors (Wilson et al. 1994; Clare and Jones 2008). The success of the errorless learning paradigms with memory-impaired individuals appeared to spawn enthusiasm regarding the application to individuals with aphasia, and a number of treatment studies have shown positive effects of errorless learning paradigms in aphasia and in PPA (e.g., Frattali 2004; Jokel et al. 2010). However, there is little evidence in the aphasia literature to suggest that constraining responses to those that are correct offers superior outcomes when compared to those that allow error. The one study that set out to directly compare errorless and errorful learning in individuals with aphasia found no significant differences (Fillingham et al. 2006). In the present study, errors were allowed to occur, and corrective feedback was provided during treatment sessions. The focus of treatment was the promotion of an active problem-solving state whereby Mr. W generated semantic information as a means to facilitate lexical retrieval. The strong positive response to treatment suggests that error production was not detrimental to learning. In fact, it could be the case that learning paradigms that constrain or limit cognitive processing are less potent than a more active approach. Additional research is needed to examine such comparisons, and the outcomes may vary depending on the cognitive status associated with different PPA variants.

In conclusion, the outcomes of this study serve to confirm other positive findings in the small, but growing body of treatment literature regarding behavioral intervention for patients with PPA. The intensive treatment approach used here is highly appropriate for PPA because it allows for a relatively rapid boost in performance over a short period of time. A positive treatment response may prompt additional self-directed or clinician-directed language maintenance activities that serve to improve language performance or stave off the effects of the neurodegenerative disease for longer periods of time. The most encouraging aspect of this study is the confirmation that neural plasticity in unaffected brain regions is available to counteract (to some extent) the language decline in primary progressive aphasia.

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